# Problem 1 : Neuronal activation

Neurons activation results in an increased need for oxygen and a large increase in blood flow that overcompensates this oxygen consumption. As a result, the venous oxyhemoglobin (rich in oxygen) concentration increases and the deoxyhemoglobin (poor in oxygen) concentration decreases .

a) Calculate the a-v (arterial-venous) difference oxygen concentration during an increase of the CBF (cerebral blood flow) of 50% assuming that the oxygen consumption is constant.

b) What is the previous effect on the concentration of the deoxyhaemoglobin in the veins?

# Problem 2: Car exchange modeling

We would like to analyze a road traffic "labeling" experiment. Let's assume that there are 200 000 cars in Geneva and 100 000 in Lausanne. There are simultaneously 400 cars per hour leaving Geneva to Lausanne and 400 cars leaving Lausanne to Geneva (average situation). We neglect the transfer time between the two cities (i.e. the amount of cars on the highway is negligible compared to the amount of cars in the cities). The original amount of red cars is supposed negligible. We also assume that no car is staying parked in either of the two cities for long time.

Let's assume now that we artificially add 50 000 red cars in Geneva at time zero (total amount of cars in Geneva=250 000 then).  The total number of car in each city stays the same during the observation time.

a) Write the differential system describing the evolution of the amount of red cars in Lausanne and Geneva with time.

b) Find its solution, corresponding with the given initial conditions.(hint: a global solution of a linear differential system can be expressed in the basis of the solutions given by the basis vectors $y_i = e^{\lambda_i t} u_i$ , where $\lambda_i$ is the ith eigenvalue and $u_i$ the ith eigenvector of the matrix A defining the linear problem : $\frac{d}{dt} X = A\,X$)

c) After a very long time, what would be the amount of red cars in Lausanne and Geneva, respectively?

d) How much time will it take to have more than 8000 red cars in Lausanne?

e) What is the percentage of red cars (called fractional enrichment) in Lausanne and in Geneva after a very long time? How do you interpret that?

# Problem 3: FDG-PET modeling / (brain) glucose metabolism

Let's consider the brain metabolic model used in PET studies for FDG modeling and subsequent glucose metabolism quantification (slide 7-9) . In this model, $C_s$ is the blood concentration of tracer (FDG), $C_{free}$ is the tissue concentration of unmetabolized FDG while $C_T$ is the concentration of FDG-6P, the phosphorylated product of FDG. $CMR_{Glc}$ is the cerebral metabolic rate of glucose and is a biochemical flux measured in µmol/g/min. The other parameters of the models $K_1, k_2$ and $k_3$ are rate constants in min$^{-1}$. They express the percentage of label leaving each pool per minute. The rate constants can be converted to fluxes by multiplying them with the concentration of the preceding pool, in µmol/g (chemical amount per gram of tissue).



7-1
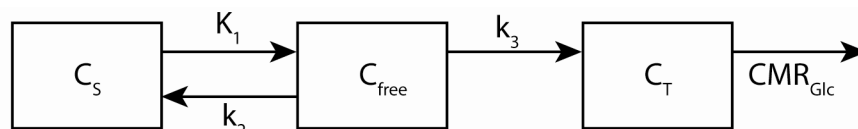
a) In a very good approximation, we can assume that the total amount of molecules (tracer + native molecule) is constant in each pool during the time of the experiment. Applying conservation of mass, show that :

$$CMR_{Glc} = C_S \frac{K_1 k_3}{k_2 + k_3}$$

Where $C_S$ is the blood concentration of glucose, a relatively easy parameter to measure experimentally.

*Hint: write the differential equation for the time evolution of the total amount of molecules in each pool and apply the mass conservation principle by forcing each differential of total concentration in tissue pools to zero.*

b) In practice, to determine $CMR_{Glc}$, the different time constants need to be estimated. This would require a continuous dynamic measurement of the radiotracer concentration in blood and tissue. To simplify this (especially for clinical studies), the Patlak graph method was developed.

To simplify the measure, let's assume that the plasma concentration of FDG (corrected for radioactive decay) follows the mathematical expression given by:

$$C_S^*(t) \ [in \ kBq/ml] = \begin{cases} \alpha \, e^{-1/\beta} \, t & for \ t \leq 1min \\ \alpha \, e^{-t/\beta} & for \ t > 1min \end{cases}$$

In a rat FDG infusion experiment, the following tracer concentrations were measured in plasma and a region of interest (ROI) for different times:

$$C_S^*(5min) = 1213.1 \frac{kBq}{ml} \qquad C_S^*(15min) = 446.3 \frac{kBq}{ml} \qquad C_S^*(30min) = 99.6 \frac{kBq}{ml}$$

$$C_T^*(40min) = 235 \frac{kBq}{ml} \qquad and \qquad C_S = 7 \ mM$$

The lumped constant (slide 7-10), is in this case: $\qquad LC = 0.71 \qquad$ (anesthetized rat brain)

Calculate the metabolic rate of glucose in this ROI using the Patlak graphical method (slide 7-9).

## Problem 4: Model Fitting Pitfalls

This Problem intends to make you aware of the pitfalls in experimental practice. In order to derive meaningful physical parameters (i.e. time constants) from experimental data, one often has to fit to a model function. This fitting is not trivial and can be error-prone.

In a PET experiment, we want to measure a saturation curve $A(1-e^{-\lambda t})$. The experiment takes 50 minutes and we can measure every 10 minutes, obtaining the following values:

| min | 5 | 15 | 25 | 35 | 45 |
|-----|-----|-----|-----|-----|-----|
| value | 0.0472 | 0.1964 | 0.4149 | 0.4259 | 0.6265 |
| fct [1] | | | | | |
| res [1] | | | | | |
| fct [2] | | | | | |
| res [2] | | | | | |

Now we want to fit to our model function. Consider the following two:

$$1 - e^{-0.02t} \qquad [1]$$
$$2 \cdot (1 - e^{-0.008t}) \qquad [2]$$

a) What is the RMSE (root mean square error, an indicator of the goodness of fit)* of the two model functions given the data points? You can use the empty fields of the table to calculate the values of the model functions and the difference to the measured values ("residuals").

b) Draw (or sketch) the two functions and the data points in one diagram. Comment on the problems you see.

c) How could one obtain more appropriate data?

\* Calculation of the RMSE: The root mean square error (error is here the difference to the model function = residual) is calculated as follows:

$$RMSE = \sqrt{\frac{\sum_1^N (\hat{\theta} - \theta)^2}{N}}$$

where $\hat{\theta}$ is the model function value, $\theta$ the measured one and N the number of samples.